METABOLISM REGULATOR IN PATIENTS WITH CHRONIC HEART FAILURE AND ANEMIA OF CHRONIC DISEASES

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ABSTRACT

Goal. To study the role of hepcidin as a regulator of iron metabolism and a mediator of inflammation in elderly and senile patients with chronic heart failure (CHF) and anemia of chronic diseases (ACD).

Material and methods. In 14 patients with CHF with ACD, 14 patients with CHF without anemia and 8 patients without CHF and anemia (control group) of elderly and senile age, the levels of hemogram parameters, ferrokinetics (serum iron, ferritin, transferrin, erythropoietin, hepcidin), inflammation [C-reactive protein (CRP), interleukin-6 (IL-6)] and the relationship between hepcidin and the named indicators.

Results. In patients of the control group, normal levels of hepcidin (9.17±0.97 ng/ml) and the only significant association of hepcidin with ferrokinetics were revealed – serum iron (r(S)=0.480, p=0.032). In the CHF group without anemia, normal levels of hepcidin (12.01±1.19 ng/ml) and two significant associations of hepcidin with ferrokinetics were also revealed – ferritin [r(S)=0.525, p=0.001] and transferrin [r(S)=-0.343, p=0.044]. In the CHF group with ACD, significantly elevated levels of hepcidin were detected (23.81±3.63ng/ml) relative to CHF without anemia (p=0.008) and the control group (p=0.003) and five significant correlations of hepcidin with hemogram parameters – hemoglobin [r(S)=-0.461, p=0.043] and the average concentration of hemoglobin in the erythrocyte [r(S)=-0.437, p=0.009]; ferrokinetics – ferritin [r(S)=0.596, p<0.0001] and transferrin [r(S) =-0.474, p=0.004]; inflammation – CRP [r(S)=0.561, p<0.0001].

Conclusion. Elevated levels of hepcidin in CHF patients with ACD and the formation of hepcidin bonds with hemogram and ferrokinetics indicators reflect its role as a regulator of iron metabolism, and the relationship with the indicator of inflammation is its role as an inflammatory mediator involved in the development of ACD in elderly and senile CHF patients.

Key words: hepcidin, chronic heart failure, anemia of chronic diseases, elderly and senile age.

INTRODUCTION

Hepcidin is secreted in the liver under the influence of proinflammatory cytokines,

mainly interleukin–6 (IL-6), which acts as a trigger for the development of anemia of chronic diseases (ACD).ACD is anemia that occurs in patients with acute or chronic activation of the immune system due to various infectious and non–communicable diseases. Other names of ACD in the literature are "inflammatory anemia" or "cytokine-induced" anemia, which reflects the connection of this anemia with the inflammatory process underlying it.

Previously, a decrease in hepcidin levels was detected in iron deficiency anemia

(IDA), and conversely, a significant increase in hepcidin levels in patients with inflammatory and autoimmune diseases, infections, sepsis, intestinal diseases, multiple myeloma, burns, as well as in patients with oncological diseases and chronic kidney diseases – that is, diseases with which ACD develops most often.

At the same time, the literature data on the level of hepcidin in patients with chronic heart failure (CHF), in the progression of which, as is known, systemic inflammation plays an important role, and which is characterized by the development of ACD, are contradictory. Some researchers have revealed an increased level of hepcidin, and others – a reduced one, in some studies it has been shown that hepcidin does not play a major role in the pathogenesis of anemia in patients with CHF, and in others, on the contrary, it has been shown that hepcidin is an important mediator of ACD in patients CHF, since it is a protein of the acute phase of inflammation and at the same time a regulator of metabolism iron provides a link between inflammation and the resulting anemia. However, the contribution of hepcidin to the development of ACD in elderly and senile patients with CHF, who are characterized by high comorbidity, including the presence of various chronic inflammatory diseases, has not been sufficiently studied. It is unclear whether hepcidin manifests its role as a regulator of iron metabolism and at the same time a mediator of inflammation in patients with CHF with ACD of elderly and senile age, and if so, to what extent. ACD in this age group This group significantly increases the risk of cardiovascular events and is more common than

other anemias, worsens the prognosis and increases mortality. The aim of the study was to study the role of hepcidin as a regulator of iron metabolism and a mediator of inflammation in elderly and senile CHF patients with ACD.

MATERIALS AND METHODS OF RESEARCH

The study included 36 elderly and senile patients (from 74 to 90 years old) with coronary heart disease: 14 CHF patients with ACD (CHF group with ACD), 14 patients with CHF without anemia (CHF group without anemia) and 8 patients without clinical manifestations of CHF and laboratory signs of anemia (control

group). Inclusion criteria. The groups of CHF with ACD and CHF without anemia included patients hospitalized for CHF of functional class III-IV (FC) according to NYHA with moderate renal impairment (serum creatinine ≤180 mmol/l) at the moment receipts. The CHF group without anemia and the control group included patients with hemoglobin levels >12 g/dl. The group of CHF with ACD included patients (both men and women) with hemoglobin levels <12 g/dl, percentage of transferrin saturation with iron (%NTJ) <20%, as with absolute iron deficiency

(ferritin level <100 mcg/l), and with functional iron deficiency (ferritin level >100 and <300 mcg/l) and the absence of proven chronic blood loss.

Exclusion criteria: megaloblastic, hemolytic, aplastic anemia, autoimmune and oncological diseases, primary kidney diseases. All participants were examined for: hemogram parameters (hemoglobin [HGB], red blood cell count [RBC], average erythrocyte volume [AEV], average hemoglobin content in erythrocyte [AHCE], average hemoglobin concentration in erythrocyte [AHCE], color index [CI]); ferrokinetic indicators (serum iron, ferritin, transferrin, erythropoietin, hepcidin); indicators of inflammation (C-reactive protein [CRP], interleukin-6 [IL-6]); for

estimates of the severity of CHF are the level of N-terminal propeptide of cerebral natriuretic peptide (NTproBNP). % NTJ was calculated using the formula: serum iron (mmol/l)×3.98/transferrin (g/l). Blood sampling was performed on an empty stomach in all patients. To assess the hematological parameters, blood samples taken in tubes with ethylenediaminetetraacetic acid were used. For the rest of the studies, serum obtained by centrifugation of blood samples during 15 min at +6°C, 3000 rpm. CRP, ferritin and transferrin were studied by immunoturbidimetric

using the SAPFIR 400 automatic analyzer method in accordance with the instructions of the reagent manufacture. Hepcidin (biologically active isoform hepcidin-25), IL-6, erythropoietin and NT-proBNP were studied by enzyme immunoassay. The following test systems were used for research: "NT-proBNP", «Erytropoitin» (EPO), «Human IL6 Platinum ELISA», "Hepcidin 25 (bioactive) ELISA".

To exclude the source of blood loss in patients CHF with ACD performed esophagogastroduodenoscopy and colonoscopy, and also examined feces for latent

blood by immunochromatographic method in accordance with the instructions of the reagent manufacturer. To assess cardiac hemodynamic disorders, all patients underwent transthoracic echocardiography on an Aplio 500 ultrasound machine

according to the standard protocol. To assess the duration of CHF, the frequency of hospitalizations per year for decompensation in CHF patients with ACD and CHF without anemia medical records (outpatient records, extracts from previous hospitalizations) were analyzed. The severity of CHF was assessed according to the NYHA classification. The severity of chronic kidney disease was assessed according to the KDOQI classification. The glomerular filtration rate (GFR) was calculated using the CKDEPI formula. The reference values of the studied indicators were determined in the control group.

The differences were considered statistically significant at $p<0.05$.

To assess the role of hepcidin as a regulator of iron metabolism and a mediator of inflammation in the development of ACD investigated the presence and strength of associations between hepcidin levels and levels of hemogram, ferrokinetics and inflammation in each group of patients. Then, correlation coefficient matrices were built for each group, and graphical correlation diagrams were used to visualize the relationships. For The Spearman correlation coefficient r(S) was used to estimate the degree of monotonic coupling. After determining the individual significance

of the correlation coefficients (that is, in pairs), the Benjimini-Yekutieli correction for multiple comparisons was used to determine their group significance in each group of patients.

THE RESULTS AND THEIR DISCUSSION

The groups of CHF patients with ACD and CHF without anemia were comparable in gender, age, functional classes (FC) of CHF (NYHA), levels of NT-proBNP, ejection fraction (EF) and cardiac comorbidity. At the same time, significant differences in extra-cardiac comorbidity were revealed: the frequency of type 2 diabetes mellitus, chronic kidney disease (stages 2 and 4), but without significant differences in GFR. In addition, there is a tendency to a difference in the incidence

of pneumonia. Since the compared groups differed in the presence of anemia

(CHF with ACD) or its absence (CHF without anemia), significant differences in hemogram parameters between the groups are expected.

Significant differences in ferrokinetic parameters were also revealed: serum iron (in patients with CHF with ACD is less, $p<0.001$), erythropoietin (in patients CHF with ACD is greater, $p=0.002$) and hepcidin (in patients CHF with ACD is higher, $p=0.008$), however, the differences in ferritin and transferrin levels were not significant.

In terms of inflammation, significant differences between the compared groups were revealed in CRP (in patients with CHF with ACD higher, $p=0.020$), while no significant differences in IL-6 were found ($p=0.456$). But at patients with CHF with ACD were found to have significantly increased IL-6 levels compared with the control group ($p=0.001$). Due to the fact that a significant increase in the level

of hepcidin, as well as CRP, which are proteins of the acute phase of inflammation, was detected only in patients CHF with ACD was not detected in patients with CHF without anemia, while at the time of hospitalization for CHF FC, the levels of NT-proBNP, PV and cardiac comorbidity of the group were comparable, in order to understand the causes of their elevated levels only in patients with CHF with ACD The frequency of inflammatory diseases, the frequency of hospitalizations per year for decompensation and the duration of CHF were analyzed. It was revealed that in the CHF group with ACD there was a high incidence of pneumonia ($p<0.05$), patients with CHF duration of more than 5 years ($p=0.002$) and the number of hospitalizations 4-5 times a year ($p=0.0002$) prevailed, and conversely, in the CHF group without anemia, patients with CHF duration of less than 5years prevailed ($p=0.02$) and the number of hospitalizations 2-3 times a year

($p=0.0002$). Ferrokinetic indicators, unlike hemogram indicators, do not have significant links between with the exception of: ferritin and erythropoietin, between which a negative relationship was revealed, hepcidin and serum iron, between which a positive relationship was revealed. Two indicators of the hemogram: HGB and RBC are associated with the indicator of ferrokinetics – serum iron, having positive associations with it. It is noteworthy that in the control

group, the indicators of inflammation do not correlate with any of the indicators of ferrokinetics, including hepcidin, and hepcidin has no direct links with any one of the indicators of a hemogram, including hemoglobin. At the same time, the connections between the ferrok-netic parameters detected in the control group (positive between hepcidin and serum iron, negative between ferritin and erythropoietin) are lost. At the same time, there are negative associations of transferrin with ferritin and hepcidin, and a positive association of ferritin with hepcidin, which were not present in the control group. That is, a new "inflammatory" triad "ferritin–transferrin-hepcidin" is being formed, all indicators

of which are proteins of the acute phase of inflammation, forming connections with hemogram parameters. Also, in the CHF group without ACD, there is a positive relationship between the indicators of inflammation: CRP and IL-6, which was not present in the control group.

At the same time, ferrokinetic indicators form numerous connections with hemogram and inflammation indicators: significant correlations of CRP with ferritin and hepcidin (positive), transferrin (negative), as well as with IL-6 (positive), and IL-

6 forms positive bonds with ferritin and erythropoietin. In the group of CHF without ACD, these connections are weak, or they did not exist.

According to the literature, various factors may be involved in the development of anemia in patients with CHF, causing a decrease in iron content in the body: microblood loss due to the use of antiplatelet agents and anticoagulants, insufficient intake of iron with food due to decreased appetite, malabsorption due to decreased absorption of the gastrointestinal mucosa, the need for repeated blood collection due to the severity of the condition, hemodilution, while in elderly and senile patients a combination of several factors is likely. But the contribution of these factors to the development of anemia in patients with CHF with ACD, it should not be considered significant, since they also occurred in patients with CHF without anemia, since the severity of CHF compared groups were comparable.

A decrease in erythropoietin synthesis due to reduced renal perfusion in CHF, as another possible mechanism for the development of ACD, is also not obvious, since in CHF patients with ACD compared with patients CHF without anemia was found to have a significantly increased level erythropoietin. It is known that systemic hypoxia, hypotension and activation of the renin-angiotensin-aldosterone system, characteristic of severe CHF, may have a greater effect on increasing erythropoietin synthesis than reduced renal perfusion due to reduced cardiac output and the negative effect of cytokines on reducing erythropoietin synthesis. An increase in erythropoietin levels can also be caused by ischemic bone marrow damage due to systemic hypoxia and impaired erythropoietin uptake. But despite the increased levels of erythropoietin, compensation anemia does not occur, which may be explained by the development of erythropoietin resistance under the influence of cytokines. Obviously, the main cause of the development of ACD in elderly and senile CHF patients should be considered systemic inflammation, characteristic according to the literature for CHF, the severity of which correlates with the severity of CHF and which causes immune activation and iron deficienc. The above is confirmed by the findings in patients CHF with ACD elevated levels of proinflammatory cytokine IL-6, as well as proteins of the acute phase of inflammation: ferritin, CRP and hepcidin, and its elevated level distinguishes ACD from IDA. It is believed that even with very mild chronic inflammatory conditions, a moderate excess of hepcidin may be enough to disrupt the balance and lead to iron deficiency and the development of ACD.

In addition, the aging process is accompanied by changes in iron metabolism and higher levels of hepcidin with a parallel increase in levels IL-6 and CRP, and pronounced inflammation, as shown, is accompanied by high levels of hepcidin and significant correlations with inflammatory markers: CRP and IL-6.

Due to the fact that elevated levels of hepcidin, as well as CRP, were detected only in patients CHF with ACD was not detected in patients with CHF without anemia,

while at the time of hospitalization, the compared groups were comparable in severity of CHF, obviously, the determining factor for the development of ACD in patients with CHF is not the severity of CHF at the time of hospitalization, but

the long duration of CHF, the high frequency of hospitalizations for decompensation, as well as the high frequency of pneumonia, which exacerbates the inflammation inherent in patients with CHF decompensation. Probably, these reasons

lead to constant cytokine aggression, which causes increased synthesis

of proteins of the acute phase of inflammation – ferritin, CRP and hepcidin.

Previously, links have been shown between iron deficiency and the frequency of repeated hospitalizations, the development of anemia and decompensation of CHF, anemia and longer hospital stay.

Therefore, taking into account the higher frequency of hospitalizations due to decompensations, as well as the longer duration of CHF detected in CHF patients with ACD than in CHF patients without anemia, it should be assumed that CHF patients with ACD, obviously, are constantly in a state of chronic inflammation, which is aggravated by decompensation of CHF, as well as with the development of pneumonia and other inflammatory diseases (urinary infection, trophic ulcers), and this state of chronic inflammation obviously persists in the period between hospitalizations, and ACD is a consequence of this chronic inflammatory process.

The detection of elevated IL-6 levels in CHF patients with AHZ and in CHF patients without anemia confirms the chronic activation of the immune system inherent in CHF decompensation, regardless of the presence or absence of anemia. Therefore, in patients with CHF with ACD, as well as in patients with CHF without anemia, the levels of ferritin, reflecting not only the iron reserves in the depot, but also being a protein of the acute phase of inflammation, are significantly increased relative to the control group.

But the severity of the systemic inflammatory response in CHF patients with ACD is obviously greater and longer. Since hepcidin synthesis is carried out mainly under the influence of IL-6, it remains unclear why, with elevated levels of IL-6 in both compared groups, the level of hepcidin in patients with CHF without anemia is not increased? Obviously, this is due to the fact that hepcidin synthesis is regulated not only by inflammation, but also by iron accumulation and erythropoiesis activity. It is also impossible to exclude participation in

synthesis of hepcidin of other proinflammatory cytokines, in particular, IL-1β, tumor necrosis factor α. It is impossible not to take into account the influence of patients' age on the development of anemia as an additional factor, since aging of the body is associated with low levels of transferrin and elevated levels of ferritin, hepcidin, IL-6 and CRP. Revealing only the fact of an increased level of hepcidin is not enough to understand its effect on all links in the development of ACD in elderly and senile CHF patients. The results of the rank correlation analysis made it possible to analyze the effect of hepcidin on hemogram, ferrokinetics and inflammation in each group of patients and evaluate its role not only as a regulator of iron metabolism, but also as a mediator of inflammation. Taking into account the data obtained, it should be assumed that in patients of the control group, that is, in the absence of CHF and anemia, hepcidin, having normal levels, realizes its role as a regulator of iron metabolism through a positive relationship with serum iron,

and through it regulates the level of hemoglobin, because it has no direct links with any of the hemogram indicators, including hemoglobin. In the CHF group without anemia, hepcidin, having also normal levels, realizes its role as a regulator of iron metabolism through a positive relationship with ferritin and a negative relationship with transferrin. At the same time, since ferritin, transferrin and hepcidin are proteins

of the acute phase of inflammation, the role of hepcidin as an inflammatory mediator is also outlined, but hepcidin obviously does not show an explicit role as an inflammatory mediator, since there are no links between hepcidin and inflammation indicators. In the CHF group with ACD, hepcidin, having elevated levels, forms five significant correlations with hemogram, ferrokinetics and inflammation, which obviously reflects the role of hepcidin as a regulator of iron metabolism, since iron depot increases through a positive association with ferritin, and iron transport decreases through a negative association with transferrin, but also as an inflammatory mediator That is, hepcidin, reacting to systemic inflammation in patients with CHF with ACD, becomes a key figure, since various types of connections, forming "bridges" between the indicators of hemogram, ferrokinetics and inflammation. Previously, the relationship of hepcidin with hemogram, ferrokinetics and inflammation in patients with AHZ was studied by many authors. Thus, the above levels of hepcidin and the negative correlation of hepcidin with hemoglobin were revealed, the positive correlation of hepcidin – with the ferrokinetic index ferritin is. However, the data on the correlations of hepcidin with indicators of inflammation (CRP and IL-6) are contradictory. Therefore, research in this direction should be continued, because studies in which, in addition to searching and analyzing the links between hepcidin levels and levels of hemogram, ferrokinetics and inflammation, attempts would be made to trace the formation of these links and trends towards their formation from the control group to CHF, and then from CHF to CHF with AHZ, which they demonstrate graphical correlation diagrams, which we have not found. Limitations of the study. It should be emphasized that this research, which is exploratory in nature, is limited to a small sample and mainly the elderly and senile age of the subjects.

CONCLUSIONS

Taking into account the inconsistency of the literature data on hepcidin levels and its role in CHF patients with ACD, it should be noted that the data obtained allow

us to characterize the role of hepcidin both as a regulator of iron metabolism and as a mediator of inflammation in elderly and predominantly senile CHF patients (median age 84 years), with "advanced" stages of CHF, long-term patients with low adherence to treatment (as indicated by frequent hospitalizations), who had at the time of their inclusion in the study not only decompensation CHF, but also complications in the form of various inflammatory diseases. The obtained data also suggest that the role of hepcidin as a regulator of iron metabolism and a mediator of inflammation may persist until old age.

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